REMARKS

Claims 3, 6, and 7 have been cancelled, without prejudice.

Claim 1 has been amended to recite "[a] process for producing canthaxanthin and echinenone, which comprises:

(a) cultivating in an aqueous nutrient medium a recombinant *Xanthophyllomyces dendrorhous (Phaffia rhodozyma)* microorganism that comprises a polynucleotide sequence that encodes a β-carotene ketolase, wherein β-carotene accumulates in the medium under aerobic conditions and wherein the cultivation is carried out at a pH in the range of from 5 to 7 and at a temperature in the range of from 18 to 22°C for 48 to 350 hours, and

(b) isolating carotenoids from the recombinant microorganism or from the medium, wherein the polynucleotide sequence is originated from a microorganism which is selected from the group consisting of *Agrobacterium aurantiacum, Alcaligenes* PC-1, *Paracoccus marcusii* MH1, a gram-negative bacteria E-396 (FERM BP-4283), and *Haematococcus pluvialis*." Support for this amendment is found in the specification at, for example, page 5, lines 18-21 and in original claims 6 and 7. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l) (8th ed. Rev. 5, August 2006, pp. 600-92 and 600-84).

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments is respectfully solicited.

INTERVIEW SUMMARY

The Examiner is thanked for the courtesies extended during a telephonic Interview conducted with the undersigned on November 1, 2007. During the interview,

the foregoing amendments and the pending rejection under 35 USC § 103 were discussed. The Examiner agreed to review the rejections in view of the amendments presented above and the remarks presented below. Therefore, in view of the amendments and remarks below, withdrawal of the rejection and allowance of the claims are respectfully requested.

Rejection Under 35 USC § 103:

Claims 1-2 and 4-8 stand solely rejected under 35 USC § 103 as unpatentable over Misawa, N. *et al.*, GenBank Accession No. 058422, Alcaligenes sp. crtW and crtZ genes for beta-carotene hydroxylase and beta-carotene ketolase, complete cds (1995) ("Misawa I") and Misawa, N. *et al.*, *"Canthaxanthin Biosynthesis By The Conversion Of Methylene To Keto Groups In A Hydrocarbon β-Carotene By A Single Gene,"* Biochemical And Biophysical Research Communications., vol. 209, no. 3, pp. 867-876 (1995) ("Misawa II") in view of Hoshino *et al.*, U.S. Patent No. 6,365,386 ("Hoshino"). (Paper No. 20070725 at 3).

The rejection respectfully is traversed.

Misawa I discloses the isolation of beta-carotene ketolase from strain *Alcaligenes* PC-1 (GenBank accession No. D58422).

Misawa II discloses that "[a] novel gene involved in ketocompound biosynthesis, designated *crtW*, was isolated from the marine bacteria *Agrobacterium aurantiacum* and *Alcaligenes* PC-1 that produce ketocarotenoids such as astaxanthin." (Abstract). Misawa II further discloses that "[w]hen this gene was introduced into *Escherichia coli* that accumulated β-carotene due to the *Erwinia* carotenogenic genes, the *E. coli* transformants synthesized canthaxanthin ...." (*Id.*). "It has been therefore

surprisingly substantiated that one gene *crtW* encodes an enzyme that catalyzes the conversion of methylene groups of a hydrocarbon β-carotene to keto groups for synthesizing canthaxanthin." (Page 874).

Hoshino discloses that "*Phaffia rhodozyma* (*P. rhodozyma*) is a carotenogenic yeast strain which produces astaxanthin." (Col. 1, lines 1-2). Hoshino further discloses "a gene and an enzyme which is involved in the last step of astaxanthin biosynthesis (i.e., from beta-carotene to astaxanthin)." (Col. 2, lines 29-31).

In making the rejection, the Examiner asserted that "1) Misawa I (GenBank) teach[es] a gene encoding beta-carotene ketolase of crtW from a *Alcaligenes PC-1*, which is 100% identical to instant application beta carotene ketolase gene; 2) Misawa II (BBRC), teach[es] a process for producing canthaxanthin echinenone by using a transformed E. coli comprising a gene encoding beta-carotene ketolase of crtW from a *Alcaligenes PC-1*, which is 100% identical to [the] instant application beta carotene ketolase gene, wherein the cells are cultured at 28 °C at a pH in which E. coli grows well i.e. pH 7-8 ...; and 3) Hoshino et al. teach[es] a process for producing astaxanthin from beta-carotene in Phaffia rhodozyma (same strain used by the instant application) comprising beta-carotene ketolase (crtW), which produces canthaxanthin from beta-carotene and crtZ gene encoding an enzyme which converts canthaxanthin to astaxanthin by cultivating said microorganism at 20 °C for overnight (i.e. 24 hr)." (Paper No. 20070725 at 5).

The Examiner acknowledged, however, that Misawa II does not teach "using Phafia rhadozyma, for producing canthaxanthin from beta-carotene comprising beta-carotene ketolase of crtW from a *Alcaligenes PC-1* ...." (*Id.*). To fill the

acknowledged gap, the Examiner relied on Hoshino and asserted that "one of ordinary skill in the art would have been motivated to use Phaffia rhodozyma instead of E. coli as taught by Hoshino et al. to produce canthaxanthin and echinenone because Phaffia, red yeast [are] usually used for the microbiological production systems for natural astaxanthin, which comprises [a] sufficient amount of natural substrate beta-carotene." (*Id.* at 5-6).

The Examiner then contended that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching[s] of Misawa et al. (GenBank), Misawa et al. (BBRC) and Hoshino et al. to produce canthaxanthin and echinenone from beta-carotene by using the beta-carotene ketolase gene (crtW) of Misawa et al. (GenBank) to transform the Phaffia rhodozyma of Hoshino et al. to produce canthaxanthin and echinenone by using the methods of Hoshino et al., which is the claimed method of the instant application." (*Id.* at 6). The Examiner further contended that "[o]ne of ordinary skill in the art would have a reasonable expectation of success because using recombinant Phaffia rhodozyma for producing canthaxanthin and echinenone is customary and widely used in the art for the biosynthesis of xanthophylls such as canthaxanthin, echinenone, astraxanthin and zeaxanthin from beta-carotene." (*Id.*).

With a view towards furthering prosecution, and as discussed during our telephonic interview of November 1, 2007, claim 1 has been amended to recite "[a] process for producing canthaxanthin and echinenone, which comprises:

(a) cultivating in an aqueous nutrient medium ***a recombinant Xanthophyllomyces dendrorhous (Phaffia rhodozyma)*** microorganism that

comprises a polynucleotide sequence that encodes a β-carotene ketolase, wherein β-carotene accumulates in the medium under aerobic conditions and ***wherein the cultivation is carried out at a pH in the range of from 5 to 7 and at a temperature in the range of from 18 to 22°C for 48 to 350 hours***, and

(b) isolating carotenoids from the recombinant microorganism or from the medium, wherein the polynucleotide sequence is originated from a microorganism **which is selected from the group consisting of *Agrobacterium aurantiacum, Alcaligenes* PC-1, *Paracoccus marcusii* MH1, a gram-negative bacteria E-396 (FERM BP-4283), and *Haematococcus pluvialis***."

It is well settled that the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152.

When patentability turns on the question of obviousness, as here, the search for and analysis of the prior art by the PTO should include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the documents relied on by the Examiner as evidence of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (April 30, 2007) (the obviousness "***analysis should be made explicit***" and the teaching-suggestion-motivation test is "***a helpful insight***" for determining obviousness) (emphasis added); *McGinley v. Franklin Sports*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). Moreover, the factual inquiry whether to combine documents must be thorough and searching. And,

as is well settled, the teaching, motivation, or suggestion to combine "***must be based on objective evidence of record***." *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002) (emphasis added). *See also* Examination Guidelines for Determining Obviousness, 72 Fed. Reg. 57526, 57528 (October 10, 2007) ("The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious.").

Respectfully, we submit that the rejection is devoid of *any* evidence - or even argument - in support of the proposed combination. All that is there is a conclusory statement that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching[s] of Misawa et al. (GenBank), Misawa et al. (BBRC) and Hoshino et al. to produce canthaxanthin and echinenone from beta-carotene by using the beta-carotene ketolase gene (crtW) of Misawa et al. (GenBank) to transform the Phaffia rhodozyma of Hoshino et al. to produce canthaxanthin and echinenone by using the methods of Hoshino et al. ...." (Paper No. 20070725 at 6). What the rejection should have done, but did not, was to explain on the record ***why*** one skilled in this art would modify the disclosure of Misawa I and II using Hoshino to arrive at the claimed method. As is well settled, an Examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done. *Takeda Chem. Indus., Ltd v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. June 28, 2007) (indicating that "it remains necessary to identify ***some reason*** that would have led a chemist to modify a known compound in a particular manner to

establish prima facie obviousness of a new claimed compound") (emphasis added); *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993). But this is precisely what the Examiner has done here. Thus, the rejection is legally deficient and should be withdrawn for this reason alone.

Notwithstanding the legally insufficient nature of the rejection, we note that the rejection is also factually insufficient to support a rejection under § 103(a). In doing so, we observe that obviousness cannot be based upon speculation, nor can obviousness be based upon possibilities or probabilities. Obviousness ***must*** be based upon facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993). Further, "to establish *prima facie* obviousness of a claimed invention, ***all claim limitations must be taught or suggested by the prior art***." MPEP § 2143.03 (citing *In re Royka*, 180 USPQ 580 (CCPA 1974)) (emphasis added).

Assuming *arguendo* that Misawa I and II are properly combinable with Hoshino, which they are not, such a combination does not produce amended claim 1, from which claims 2, 4-5, and 8 depend. As acknowledged by the Examiner, Misawa I "do[es] not teach the use of [a β-carotene ketolase gene] for a process for producing canthaxanthin and echinenone," and Misawa II "do[es] not teach the use of transformed Phaffia rhodozyma by the said gene for producing canthaxanthin and echinenone." (*See* Paper No. 20060627 at 10 and Paper No. 20070725 at 5). Simply put, Misawa I and II alone, or in combination, do not disclose or suggest currently amended claim 1.

Unfortunately for the Examiner, Hoshino fails to fill this factual gap. As

conceded by the Examiner in Paper No. 20060627 at 10, Hoshino "do[es] not disclose the isolation of the beta-carotene ketolase gene from Alcaligenes PC-I [ ] and expression of beta-carotene ketolase in said recombinant microorganism using control sequences or culturing the recombinant microorganism ***for 48-350 hours***." (Paper No. 20060627 at 10) (emphasis added). Hoshino discloses the cloning of astaxanthin synthase. In Hoshino, a specific mutant, *Phaffia rhodozyma* ATCC 96815, which was blocked for the reaction from β-carotene to astaxanthin, was used as a transformation host. This mutant was transformed with genetic material from the chromosome of a wild-type strain of *Phaffia rhodozyma* ATCC 96594 for the purpose of identifying a genetic fragment complementing the reaction from β-carotene to astaxanthin in *Phaffia rhodozyma*. (Col. 8, lines 13-28). Thus, the mutation in the *Phaffia rhodozyma* strain ATCC 96815 was obtained by the gene from another strain of *Phaffia rhodozyma*. Hoshino fails to disclose or suggest inserting a polynucleotide sequence from ***another genus or strain of bacteria or algae*** into *Phaffia rhodozyma*, let alone the specific microorganisms, ***Agrobacterium aurantiacum, Alcaligenes*** **PC-1,** ***Paracoccus marcusii*** **MH1, a gram-negative bacteria E-396 (FERM BP-4283), and** ***Haematococcus pluvialis, wherein the cultivation is carried out at a pH in the range of from 5 to 7 and at a temperature in the range of from 18 to 22°C for 48 to 350 hours***. Thus, Hoshino falls short of filling the factual gap left by Misawa I and II. For this reason also, the rejection should be withdrawn.

The rejection is also devoid of any discussion of the dependent claims. Accordingly, the record is devoid of any evidence that the Examiner individually considered the dependent claims. It is axiomatic, however, that a dependent claim is

not *per se* unpatentable by a document that allegedly makes unpatentable the base claim. Accordingly, "[e]xaminers are reminded that a dependent claim is directed to a combination including everything recited in the base claim and what is recited in the dependent claim. ***It is this combination that must be compared with the prior art, exactly as if it were presented as one independent claim.***" MPEP § 608.01(n) (8th ed., Rev. 5, Aug. 2006, pp. 600-91). This the Examiner has not done. Accordingly, the rejection is also both factually and legally deficient as to the dependent claims. For this additional reason, the rejection should be withdrawn as to the dependent claims.

In view of the foregoing, it is respectfully submitted that the rejection has been rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

Accordingly, for the reasons set forth above, entry of the amendments, withdrawal of the rejection, and allowance of the claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on November 28, 2007.

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